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Haemodynamic Effects of Nitroglycerin in Patients with Mitral Valvular Disease

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Nitrites are widely used for the treatment of angina pectoris, but their mechanism of action is still not clear. Animal experiments have shown that nitrites dilate arteries, arterioles, capillaries, and veins (for a review: see Charlier, 1961). Most workers feel that nitroglycerin acts by dilating coronary vessels, though such an effect has been difficult to show in patients with coronary heart disease. Moreover, Gorlin *et al.* (1959), Weiss, Wilkins, and Haynes (1937), Wilkins, Haynes, and Weiss (1937), and Johnsson, Henning, and Åblad (1965) have shown that the most important circulatory effect of nitrites in man is probably a dilatation of peripheral veins, which may lead to a fall in central blood volume and a reduction of the work of the heart. Others, e.g. Christensson, Karlefors, and Westling (1965), maintain that this may be a sufficient explanation for the relief of anginal pain, since they found a reduced stroke volume after nitroglycerin, particularly when the drug was given during anginal pain provoked by sitting exercise. However, these findings were not confirmed by Hoeschen *et al.* (1966): they found increased cardiac output and stroke volume when nitroglycerin was given to patients with angina pectoris under experimental conditions which appear similar to those of Christensson *et al.* (1965). It has also been observed by O. Müller (1963, personal communication), Arborelius *et al.* (1968), and Najmi *et al.* (1967) that nitroglycerin may prevent anginal pain during supine exercise without a reduction of cardiac output, but with reduced pressures in the lesser circulation. Variations in the patients and the experimental methods may possibly explain the different results, but nevertheless these findings and those of Hoeschen *et al.* (1966) appear to cast doubt on the theory that nitroglycerin acts *only* by reducing the work of the heart.

New light on the haemodynamic consequences of coronary insufficiency was obtained by Müller and Rørvik (1958). They found that anginal pain was associated with increased pressures in the left atrium and the pulmonary artery. After nitroglycerin the pressures were quickly lowered to normal. The effects of nitroglycerin and related substances on other conditions with raised pressures in the pulmonary circulation have also been studied. Thus, reduction of pressures in the pulmonary artery and the left atrium has been obtained in patients with left ventricular failure due to hypertension, and in patients with mitral valvular disease (Johnson, Gross, and Hale, 1957; Johnson, Fairley, and Carter, 1959; Fremont, 1961; Kleinerman *et al.*, 1964).

The present report contains further observations on the action of nitroglycerin in patients with mitral valvular disease, with particular reference to the effects during exercise. The investigation was initiated by the favourable clinical effects obtained by nitroglycerin in patients with symptoms of imminent pulmonary oedema in connexion with catheterization.

Subjects and Methods

Observations were made on 26 patients with mitral valvular disease, judged to be predominantly stenosis, who underwent a routine pre-operative assessment.

Right heart catheterization was carried out in the supine position, after premedication with a small dose of barbiturate; the examination was performed in the morning and the patients were not given breakfast.

A double-lumen catheter was used for simultaneous recording of pressures in the pulmonary artery and in the wedge position (PCV pressure). A polyethylene

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TABLE I

HAEMODYNAMIC OBSERVATIONS IN 12 PATIENTS WITH MITRAL VALVULAR DISEASE AND SINUS RHYTHM DURING CONTINUOUS WORK IN SUPINE POSITION BEFORE AND AFTER ADMINISTRATION OF 0·5 MG. NITROGLYCERIN SUBLINGUALLY

Sex	Age (yr.)	Heart rate (beats/min.)	Cardiac output (l./min.)		Stroke volume (ml.)		Pressures (mm.Hg)							Oxygen consumption (ml./min.)	Art. ven. oxygen diff. (ml./l.)
							PCV	Pulm. art.			Brach. art.				
			BSP	Fick	BSP	Fick	M	S	D	M	S	D	M		
F	51	B 159	5·4	—	34	—	37	76	55	55	201	105	149	—	88
	—	A 163	5·0	—	31	—	21	54	21	30	178	103	127	—	83
F	57	B 101	7·3	—	72	—	15	47	20	30	173	70	108	—	72
	—	A 109	6·1	—	56	—	9	32	10	18	140	63	96	—	83
F	44	B 107	9·0	8·2	84	77	34	55	36	45	169	100	128	642	78
	—	A 111	8·8	8·4	79	76	28	51	27	38	161	96	119	644	77
F	43	B 105	9·2	10·1	88	96	22	62	27	42	153	83	110	677	67
	—	A 110	8·0	8·0	73	73	13	40	17	28	147	78	95	642	80
F	58	B 142	9·5	12·8	67	90	32	—	—	43	154	70	105	779	61
	—	A 152	9·3	10·1	61	66	25	—	—	37	151	73	102	787	78
F	52	B 118	7·9	9·1	67	77	32	56	26	41	150	80	113	734	81
	—	A 127	8·4	9·8	66	77	22	43	20	22	142	84	107	786	80
F	51	B 121	8·4	—	69	—	22	—	—	32	167	95	131	—	73
	—	A 136	7·9	—	53	—	13	—	—	18	170	100	122	—	71
F	58	B 134	9·4	9·6	70	72	30	—	—	42	190	97	144	854	89
	—	A 134	8·2	9·0	61	67	10	—	—	20	164	85	111	824	92
M	58	B 90	10·0	9·6	111	107	22	55	25	35	152	80	101	847	88
	—	A 95	7·7	9·6	81	101	13	36	15	23	116	67	91	860	90
M	54	B 91	10·7	9·4	118	103	34	86	34	55	138	67	95	770	82
	—	A 95	11·2	10·2	118	107	23	55	22	35	130	63	86	880	86
M	49	B 93	10·8	10·9	116	117	31	81	35	52	127	63	86	970	89
	—	A 99	10·8	10·4	109	105	22	61	25	38	115	57	78	970	93
M	49	B 100	8·9	10·7	89	167	39	—	—	56	153	83	112	1020	95
	—	A 104	7·4	8·5	71	82	15	—	—	29	135	83	103	940	110

PCV = Pulmonary artery wedge pressure.
BSP = Bromsulphalein.
S, D, M = Systolic, diastolic, and mean pressure, respectively.

A = After nitroglycerin.
B = Before nitroglycerin.

catheter was introduced into the brachial artery percutaneously. Oxygen consumption was measured by collecting expired air in a Douglas bag for 7 minutes at rest and 4 minutes during exercise. Respiratory gases were analysed according to Scholander (1947). Cardiac output was measured by the Fick principle and also by the dye-dilution technique, using bromsulphalein (BSP) as an indicator (Wassén, 1956). Both methods were used simultaneously when possible.

Pressures were measured by inductance or capacitance manometers and recorded together with the electrocardiogram on an ink-writing electrocardiogram.*

Examinations were carried out on 6 patients with sinus rhythm and 8 with atrial fibrillation at rest. Cardiac output and pressures were determined, and immediately after this 0·5 mg. nitroglycerin was given sublingually. New determinations were made 3 to 5 minutes after the tablet had dissolved.

Exercise tests were carried out on 12 patients in sinus rhythm (Table I). The supine patient pedalled an electrically-braked bicycle ergometer,† with a centre of rotation approximately at heart level. The work load was 300 kpm./min. for men and 200 kpm./min. for women. The patients exercised for 10–15 minutes. The first haemodynamic measurements were carried out after about 5 minutes of continuous work. Nitroglycerin was then given while the patient continued working. New determinations of pressures and cardiac output were made 4 to 6 minutes after the nitroglycerin had been given.

* Mingograph, AB Elema, Sweden.
† AB Elema.

In order to evaluate the possible spontaneous changes in the haemodynamic conditions during continuous exercise, duplicate determinations were made in a series of patients with mitral valvular disease (Gustafson, 1966). The interval between the two determinations was about 5 minutes. The results in 14 patients with sinus rhythm are given in Table II.

Results

The predominant haemodynamic effect of nitroglycerin during exercise was the reduction of both pulmonary and PCV pressures (Tables I and II). The reduction of systemic arterial pressure was also statistically significant. Cardiac output was slightly decreased in those patients to whom nitroglycerin was given in comparison with the patients to whom it was not given. The stroke volume was more reduced since the heart rate increased after nitroglycerin. The arteriovenous oxygen difference increased slightly.

A difference in the behaviour of the cardiac output and stroke volume became apparent if the patients were divided in two groups, according to the level of the PCV pressure after nitroglycerin. In the 6 patients with the lowest PCV pressures after nitroglycerin (average value 12 mm. Hg against 25 mm. Hg before the drug), cardiac output decreased by 1·3 l./min. and stroke volume by 17 ml., on the average. In the remaining 6 patients PCV pressures fell from 33 to 25 mm. Hg. In this group

TABLE II

SUMMARY OF HAEMODYNAMIC EFFECTS OF NITROGLYCERIN DURING EXERCISE IN PATIENTS WITH MITRAL VALVULAR DISEASE (SINUS RHYTHM)

	Control group				Nitroglycerin group			
	Mean initial value	No. of observations	Change in repeated test Mean ± S.E.M.	p value	Mean initial value	No. of observations	Change in repeated test Mean ± S.E.M.	p value
Heart rate (beats/min.)	101	14	+3·6±0·82	<0·001	113	12	+6·2±1·11	<0·001
Cardiac output (l./min.)								
BSP	8·35	14	−0·21±0·10	—	8·9	12	−0·73±0·22	<0·01
Fick	8·53	14	+0·01±0·12	—	10·0	8	−0·90±0·39	—
Stroke volume (ml.)								
BSP	83·5	14	−4·4±1·03	<0·001	82·1	12	−10·1±2·47	<0·01
Fick	85·2	14	−2·6±1·03	—	94	8	−10·7±3·6	<0·05
Mean pressure (mm.Hg)								
PCV	19·6	14	−2·3±0·36	<0·001	29·2	12	−11·3±1·64	<0·001
Pulmonary artery	30·1	14	−1·9±0·41	<0·001	44·0	12	−16·9±1·92	<0·001
Brachial artery	104·1	14	−2·90±0·71	<0·01	155·2	12	−12·1±2·34	<0·001
Oxygen uptake (ml./min.)	671	14	−1·0±10·6	—	810	8	−16±11·3	—
Arteriovenous oxygen difference (ml./l.)	80·1	14	−0·4±1·23	—	80·3	12	+5·8±1·91	<0·05

cardiac output was unchanged and the average stroke volume fell by 3·7 ml. only.

The haemodynamic changes after nitroglycerin at rest were in principle the same as those described above during exercise.*

In 7 patients, who had respiratory distress and objective signs of imminent pulmonary oedema at rest or during exercise, the symptoms disappeared quickly after nitroglycerin, in pace with the reduction of PCV pressure.

Discussion

The effects of nitroglycerin in the present series of patients with mitral valvular disease were in the main confined to a reduction of pulmonary arterial and PCV pressures. The calculated pulmonary vascular resistance was reduced more than the systemic vascular resistance. These observations are in accordance with those reported by Dresdale *et al.* (1963) regarding the effect of isosorbide dinitrate on the haemodynamics in patients with mitral stenosis.

One possible mode of action of nitroglycerin in mitral stenosis is on the peripheral veins (capacitance vessels), thereby reducing the blood flow into the lesser circulation, with a consequent drop in pulmonary and left atrial pressure. It is also possible that nitroglycerin reduces the tone in the pulmonary veins; this would also decrease the left atrial pressure. The latter mechanism would fit in with the reports of disturbed ventilation, decreased compliance, and increased pulmonary blood volume (Dresdale *et al.*, 1963; Kleinerman *et al.*, 1964; Ferrer *et al.*, 1966).

It seems likely that the pressure gradient over the mitral valve was reasonably well maintained in those patients in whom nitroglycerin caused a moderate fall in PCV pressure. Left ventricular diastolic pressure would thus decrease in parallel with the left atrial pressure. With a more pronounced effect, stroke volume and cardiac output also fell, indicating a reduction in effective pressure gradient, possible because of approaching a "minimal" left ventricular diastolic pressure.

We would like to suggest that the mechanism of action of nitroglycerin is the same in mitral valvular disease and in coronary heart disease. The different results as regards cardiac output and stroke volume obtained by O. Müller (1963, personal communication), Christensson *et al.* (1965), Hoeschen *et al.* (1966), Arborelius *et al.* (1968), and Najmi *et al.* (1967) should, in our opinion, be regarded as quantitatively rather than qualitatively different.

In this connexion, the important problem of a generally increased venous tone in patients with manifest or imminent cardiac failure should be discussed. It is even possible that the increase in venous tone in certain patients is more pronounced in the pulmonary veins. Raphael and Steiner (1966) have shown that the motor activity of the pulmonary veins is changed in patients with mitral stenosis. It is well known that an increase in venous tone caused by sympathetic stimulation can bring about pulmonary oedema in such patients, as well as in patients with latent left ventricular failure from any cause. In such patients the administra-

*The results of these measurements are not given here, but the authors will be pleased to send them to anyone who is interested.

tion of nitrites can be said to interfere with an important patho-physiological "trigger" mechanism. A similar mechanism may well operate in attacks of angina pectoris, particularly those caused by "emotional tension".

Dresdale *et al.* (1963) concluded: "The impression is that the nitrates have an effect on the pulmonary vascular bed when there is pulmonary hypertension secondary to increased pulmonary venous pressure." Our investigations support this statement as regards the effect of nitroglycerin at rest, and supplement the previous observations by measurements during exercise, which show in principle the same effect.

An important stimulus for the present work was the repeated clinical observation that the administration of nitroglycerin to patients with imminent pulmonary oedema from any cause, including mitral valvular disease, had a good effect on the subjective symptoms and also produced an objective improvement, with disappearance of physical signs. This effect has been obtained not only during heart catheterization but also during long-continued treatment at home.

Summary

The haemodynamic response to nitroglycerin sublingually was examined at rest or during exercise in patients with mitral valvular disease. Six patients with sinus rhythm and 8 patients with atrial fibrillation were studied at rest, and 12 patients with sinus rhythm were studied during exercise.

The dominant finding was a reduction in pulmonary arterial and pulmonary artery wedge pressures. At the same time, subjective and objective symptoms of pulmonary engorgement were reduced in 7 patients.

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